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EXAMINER

FISHER, ABIGAIL L

ART UNIT

PAPER NUMBER

1616

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/679,581	DENNIS ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	ABIGAIL FISHER	1616	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 12 November 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 25,27-43,45 and 47 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 25,27-43,45 and 47 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

Receipt of Amendments/Remarks filed on November 12 2008 is acknowledged. Claims 1-24, 26, 44 and 46 were/stand cancelled. Claims 25 and 45 were amended. Claims 25, 27-43, 45 and 47 are pending.

### *Claimed Interpretation*

For the purpose of applying art, the recitation of the intended use of the claimed invention, for intravenous delivery in the instant application is not given patentable weight. A recitation of the intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. **Note:** MPEP 2111.02 [R-3]

Claims 25 and 45 and the claims that depend from claims 25 and 45 contain the transitional language “consisting essentially of”. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, “consisting essentially of” will be construed as equivalent to “comprising.” **If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of “consisting essentially of,” applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention.** *PPG Industries Inc. V Guardian*

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*Industries Corp.* 48 USPQ2d 1351 (Fed. Cir. 1998) and *In re De Lajarte* 337 F.2d 870, 143 USPQ 256 (CCPA 1964) **See MPEP 2111.03.**

The instant specification does not define the term “consisting essentially of” in a manner that would allow one skilled in the art to determine what basic and novel characteristics are being materially affected. Applicants claim a microemulsion comprising an oil phase and an aqueous phase wherein the oil phase consists essentially of an oil-soluble drug, a long chain polymer surfactant, a short chain fatty acid surfactant. The invention of Hauer et al. comprise a hydrophilic phase (aqueous phase), a lipophilic phase (oil phase), and a surfactant (including both hydrophilic and lipophilic surfactants). Other components taught and exemplified that can be included are thickeners and hydrophilic and lipophilic solvents.

### **Claim Rejections - 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 25, 27-30, 34, 37-38, 40-41, 43 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. (US Patent No. 6024978) as evidenced by The Merck Index (1989).**

#### **Applicant Claims**

Applicant claims a microemulsion comprising an oil phase and an aqueous phase wherein the oil phase consists essentially of an oil-soluble drug, a long chain polymer surfactant and a short chain fatty acid surfactant. The particle size of the oil phase is from 10 nm to 100 nm (0.01 to 0.1  $\mu\text{m}$  or 100 to 1000 angstroms).

#### **Determination of the Scope and Content of the Prior Art (MPEP §2141.01)**

Hauer et al. is directed to pharmaceutical formulations comprising cyclosporin. Cyclosporin is disclosed as a very hydrophobic compound (column 3, line 26). The microemulsions comprise a hydrophilic phase, a lipophilic phase and a surfactant along

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with cyclosporin. Cyclosporin is present in an amount from 1 to about 30% (column 17, lines 12). Example 5.2 (column 30) is directed to a thickened emulsion pre-concentrate type comprising cyclosporin, Pluronic F68 and sodium laurylsulphate. Pluronic F68 is disclosed by applicant (page 15 of the specification) as a suitable long chain polymer surfactant. Hauer et al. disclose that microemulsions obtained from the microemulsion pre-concentrates having an average particle (droplet) size of less than 1500 angstroms preferably less than 1000 angstroms and down to about 150 or 200 angstroms. It is disclosed that the microemulsions of Hauer et al. enable effective cyclosporin dosing with concomitant enhancement of resorption/bioavailability as well as reduced variability in individual patients (column 5, line 3-4). Dosage types of the formulation include topical and oral dosage forms (abstract). It is disclosed in addition to cyclosporin that the composition may include one or more further ingredients such as alpha-tocopherol. The use of a tocopherol is disclosed as being particular advantageous (column 13, lines 35-41).

The Merck Index indicates that sodium lauryl sulfate contains 12 carbons thereby fitting applicant's definition of a short chain fatty acid surfactant.

**Ascertainment of the Difference Between Scope the Prior Art and the Claims  
(MPEP §2141.012)**

Hauer et al. do not exemplify a microemulsion with Pluronic F68 and sodium laurylsulfate. Hauer et al. do not exemplify a microemulsion comprising cyclosporin and alpha-tocopherol. However, Hauer et al. do exemplify an emulsion with these surfactants and indicate that the addition of alpha-tocopherol is preferable.

***Finding of Prima Facie Obviousness Rational and Motivation  
(MPEP §2142-2143)***

It would have been obvious to one of ordinary skill in the art to formulate example 5.2 as a microemulsion. One of ordinary skill in the art would have been motivated to formulate a microemulsion of this type as the surfactants, Pluronic F68 and sodium laurylsulphate are disclosed as being suitable surfactants and are exemplified in an emulsion type formulation. One of ordinary skill in the art would have been motivated to choose these surfactants from those listed as suitable because Hauer et al. exemplify utilizing these surfactants in combination.

It would have been obvious to one of ordinary skill in the art to further add alpha-tocopherol (vitamin E) to the microemulsion. One of ordinary skill in the art would have been motivated to add tocopherol as it is disclosed by Hauer et al. as being suitable and advantageous.

Regarding instant claim 43, Hauer et al. disclosed that the microemulsions enable effective cyclosporin dosing with concomitant enhancement of resorption/bioavailability as well as reduced variability in individual patients. Therefore, it is the microemulsion that is controlling the drug transfer rate.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

**Claims 31-33, 39, 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. in view of Constantinides (WO 9408610, cited on PTO Form 1449).**

### **Applicant Claims**

Applicant claims that the long chain polymer surfactant component is a poloxamer and the short chain fatty acid surfactant component is a laurate. Applicant claims that the interfacial tension is less than 0.1 dynes per cm. Applicant claims that the total amount of both surfactants does not exceed 4.65%. Applicant claims that the ratio of long chain to short chain surfactant is from 10:100 to 25:80 wt/wt.

### **Determination of the Scope and Content of the Prior Art (MPEP §2141.01)**

The teachings of Hauer et al. are set forth above. Specifically Hauer et al. disclose microemulsions. Surfactants exemplified include a poloxamer, Pluronic F68, and sodium laurylsulphate.

### **Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)**

Hauer et al. do not specify that the surfactant can be a laurate. Hauer et al. do not specify the amount of the surfactants are less than 4.65% or that the ratio of long to short chain surfactant is from 10:100 to 25:80 wt/wt. Hauer et al. do not specify the interfacial surface tension. However, these deficiencies are cured by Constantinides.

Constantinides is directed to microemulsions comprising an oil, a mixture of high and low HLB surfactants (abstract). It is disclosed that it has been long recognized that low interfacial tension contributes to the thermodynamic stability of microemulsion. To



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achieve this, the surfactant should preferably exhibit low solubility in both the oil and water phases and be preferentially absorbed at the water-oil interface with concomitant lower of the interfacial tension. An interfacial tension of less than  $2 \times 10^{-2}$  dyn/cm results in stable microemulsions (page 1, lines 23-28). It is disclosed that the incorporation of medium-chain fatty acid salts have been found to further enhance the absorption of a biologically active agent (page 5, lines 29-30). Medium chain is defined as fatty acyl chain having from 6 to 12 carbon atoms (page 5, lines 36-37). A particular combination of high HLB surfactant combination exemplified is Tween 80 and sodium laurate (example 7). It is disclosed that high HLB surfactants such as the medium chain fatty acids and Tween 80 (which is indicated by Applicant as being a suitable long chain fatty acid surfactant (page 16 of the specification)) are present in an amount from about 5 to about 75% (page 15, lines 5-7). Constantinides indicates that one of skill in the art would know that in order to accommodate a larger amount of a hydrophilic phase then this will have be matched by an increase in the relative amount of high HLB surfactant (page 15, lines 13-16).

***Finding of Prima Facie Obviousness Rational and Motivation  
(MPEP §2142-2143)***

It would have been obvious to one of ordinary skill in the art to combine the teachings of Hauer et al. and Constantinides and utilize sodium laurate in combination with another high HLB surfactant such as Tween 80 or Pluronic F68. One of ordinary skill in the art would have been motivated to utilize sodium laurate in combination with another high HLB surfactant as medium chain fatty acid salts have been found to further enhance the absorption of biologically active agents as taught by Constantinides.

It would have been obvious to one of ordinary skill in the art to optimize the amount and ratio of the high HLB surfactants present in the microemulsion. One of ordinary skill in the art would have been motivated to optimize the amount and ratio depending on the surfactants utilized as the well as the amount of a hydrophilic phase. Constantinides indicates that the larger amount of a hydrophilic phase the more high HLB surfactant needed, therefore, the smaller the hydrophilic phase the less high HLB surfactant needed. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. **In re Aller, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).**

Regarding the interfacial tension, Hauer et al. is silent as to the interfacial tension. Constantinides disclosed that it has been long recognized that low interfacial tension contributes to the thermodynamic stability of microemulsion. To achieve this, the surfactant should preferably exhibit low solubility in both the oil and water phases and be preferentially absorbed at the water-oil interface with concomitant lower of the interfacial tension. An interfacial tension of less than  $2 \times 10^{-2}$  dyn/cm results in stable microemulsions (page 1, lines 23-28). Therefore, when desiring a stabile microemulsion it would have been obvious to one of ordinary skill in the art to select surfactants that exhibit low solubility in both oil and water phases as taught by Constantinides.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

**Claims 35-36 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. as evidenced by The Merck Index (1989, page 1364) in view of The Merck Index (1989, page 478)**

#### **Applicant Claims**

Applicant claims that the drug is an anesthetic. Applicant claims that the drug is an aryl containing molecule. Applicant claims that the drug is an oil-soluble vitamin. Applicant claims that the drug is a mixture of the base form and the salt form of the drug. Applicant claims that the microemulsion comprises at least two oil-soluble drugs.

#### **Determination of the Scope and Content of the Prior Art (MPEP §2141.01)**

The teachings of Hauer et al. are set forth above. Hauer et al. is to the delivery of cyclosporin via a microemulsion. It is disclosed that Cyclosporin is applicable to a variety of inflammatory conditions such as arthritis (column 1, lines 61-63).

#### **Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)**

Hauer et al. do not specify that anesthetic or aryl containing molecules can be included in the microemulsion. Hauer et al. do not specify that the drug is a mixture of the base form and the salt form of the drug. However, this deficiency is cured by The Merck Index.

The Merck Index indicates that dibucaine which is a local anesthetic is available as the hydrochloride salt as well the base form. The structure of dibucaine contains an aryl group.

***Finding of Prima Facie Obviousness Rational and Motivation  
(MPEP §2142-2143)***

It would have been obvious to one of ordinary skill in the art to combine the teachings of Hauer et al and The Merck Index and utilize dibucaine in the microemulsion. One of ordinary skill in the art would have been motivated to add dibucaine because it is taught by Hauer et al. that ciclosporin is used to treat inflammatory conditions such as arthritis. Therefore, the incorporation of an anesthetic would have an additive effect in treating the symptoms of the condition sought to be treated by Hauer et al.

It would have been obvious to one of ordinary skill in the art to utilize both the base form and salt form of the anesthetic. One of ordinary skill in the art would have been motivated to utilize this form because both forms are known and the incorporation of both forms would allow for the increased solubility of the drug as the base form would be more oil soluble while the salt form would be more water soluble.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

### ***Response to Arguments***

Applicants argue that Hauer teach a microemulsion pre-concentrate that includes a hydrophilic phase, a lipophilic phase and a surfactant and that the microemulsions may be obtained by contacting the pre-concentrate with water or another aqueous medium. The lipophilic phase includes a solvent which is devoid of any surfactant function. The instant claimed microemulsion composition includes an oil phase and an aqueous phase, where the oil phase consists essentially of an oil-soluble drug, a long chain polymer surfactant component and a short chain fatty acid surfactant component.

Applicants' arguments filed November 12 2008 have been fully considered but they are not persuasive.

Firstly it is unclear what applicants believe is excluded by the instant claim language of consisting essentially of. The example pointed to by the examiner, specifically 5.2 comprises cyclosporine (oil soluble drug), transcitol (hydrophilic solvent), Pluronic F68 and sodium laurylsulphate (which are either explicitly taught by applicant as suitable surfactants or fit their definition) and sodium carboxymethylcellulose (which is a thickener). This pre-concentration can then be combined with water or other aqueous medium to form an emulsion. While, this particular example is to an emulsion, microemulsions are exemplified as well and it would have been obvious to one of ordinary skill in the art to manipulate the formulation to form a microemulsion. While Hauer et al. do teach that the lipophilic phase can comprise a solvent that is devoid of surfactant function, incorporation of surfactants is taught and exemplified. If applicants contend that the additional materials that can be

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incorporated (thickener and solvent) in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of the additional components would materially change the characteristics of applicant's invention

Therefore, the rejection is maintained since applicant has not provided any persuasive arguments to overcome the rejection.

### ***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Abigail Fisher  
Examiner  
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AF

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